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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 12162003

Application Number: 09/714,882
Filing Date: November 16, 2000
Appellant(s): TURNER ET AL.

Lance K. Ishimoto
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7 October, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is essentially correct, except that the asserted utilities for the claimed invention are currently being disputed.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellants provide a statement in the brief that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

5,194,596 Tischer et al. 3-1993

Benjamin et al., 1998, Development 125:1591-1598., see Abstract and pp. 1594-1596.

Vukicevic et al. 1996, PNAS, USA 93:9021-9026.

Massague,1987, Cell 49:437-8.

Pilbeam et al., 1993, Bone 14:717-720.

Biunno et al. Sel1, the human homolog of C. elegans sel-l: refined physical mapping, gene structure and identification of polymorphic markers. 2000, Human Genetics, Vol. 106, pages 227-235.

Yan et al., Two-Amino Acid Molecular Switch in an Epithelial Morphogen That Regulates Binding to Two Distinct Receptors. Science, Vo. 290, Oct. 20, 2000, pages 523-527.

Baron et al., Molecular Membrane Biology, 2002, Vol. 19, pages 27-38.

Portin, P., Hereditas, 2002, Vol. 136, No. 2, pages 89-96.

Baron et al., Seminars in Cell and Developmental Biology, April, 2003, Vol. 12, No. 2, pages 113-119.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

Claims 1-8 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial and credible asserted utility or a well established utility.

Claims 1-8 are drawn to the nucleic acid molecules comprising the nucleic acid sequence of SEQ ID NO: 1 or nucleic acids encoding the protein of SEQ ID NO: 2, and the splice variants having the amino acid sequences of SEQ ID NOS: 4, 6, 8 and 10, identified as NHPs (novel human proteins). The instant specification discloses that the full length NHP of SEQ ID NO: 2 is a 689 amino acid protein, and that the protein of SEQ ID NO: 2 shares structural similarity with animal *Notch* ligands, and particularly SEL-1 proteins, which are negative regulators of Notch family receptors. The specification asserts that the NHP protein is a member of the *Notch* ligand family due to this amino acid homology Sel-1. Biunno et al., Human Genetics, Vol. 106, pages 227-235, 2000, discloses the human Sel-1 protein, alignment with SEQ ID NO: 2 of the instant invention shows that there are regions of homology over most of the length of the protein, from amino acids 96-688 of SEQ ID NO: 2, and the entire percent similarity between these two proteins is 46%. However, the NHP nucleic acid molecules or encoded proteins do not have any specific and substantial utility, or a well established utility, as determined according to the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001.

The instant application describe the uses and methods of the invention, and state that the nucleic acids and proteins can be used in methods such as screening assays to identify receptors, binding proteins, agonists or antagonists which may potentially be drugs, making transgenic

animals to also use in screening assays, use of the protein to raise antibodies, use of the nucleic acids to identify mutant alleles, identify polymorphisms, determining the structure of a given locus/allele, expressing the nucleic acid in order to make the protein, or as probes to screen for libraries and isolate clones, or asses gene expression patterns, for example.

However, none of these uses are considered to be specific or substantial utilities for either the nucleic acid molecules or the protein encoded by them. Methods such as identification of receptors, agonists or antagonists, screening for homologous genes, use to identify polymorphisms or alleles, use to recombinantly produce protein or use to generate antibodies are considered general methods applicable to any nucleic acid and/or protein, and are not considered specific.

The instant application also teaches that the nucleic acids, antisense nucleic acids, protein and associated antibodies, agonists, antagonists can be used either diagnostically to identify mutations, disorders or diseases, and used diagnostically or therapeutically to identify and treat diseases or disorders such as Alzheimer's Disease, diabetes, stroke, vascular dementia, and conditions requiring modulation of fat and cholesterol metabolism such as coronary artery disease.

However, the assertion that the nucleic acids/and or proteins of the instant invention can be used in the diagnosis or treatment of diseases or disorders is also not a specific and substantial utility, and is based on the assumption that the protein is a ligand in the *Notch* ligand family, which as a family are involved in myriad biological pathways and activities. Biunno et al. teach that Sel-1 is ubiquitously expressed in human fetal tissues, but it exhibits high mRNA levels only in adult pancreas and in islets of Langerhans (see page 2), while the instant specification teaches

that NHP is expressed in human testis cells. Biunno et al. teach that SEL1 resides on human chromosome 14q24.3-q31, a region linked to an insulin-dependent diabetes mellitus locus, IDDM 11, and on page 2, state that several correlations between mutations in Notch-like genes and pathways to human diseases have been described, and three human disorders including a neoplasia, a late onset neurological disease (CADASIL) and a developmental disorder (the Alagille syndrome) are associated with mutations in, the *Notch1*, *Notch3* and *Jagged1* genes, respectively, highlighting the broad spectrum of Notch activity in humans. On page 7, Biunno et al. state:

> We are studying various aspects of SEL1, both at the structural and functional level, in order to reach a hypothesis regarding the exact role of this protein in cell-cell interaction. At the same time, we are performing association studies in type I diabetic clinical material, such as case control or families, to link polymorphisms and haplotypes of polymorphisms to the SEL1L chromosomal region in order to verify if the gene is responsible for diabetes mellitus type I.

Though sequence homologies may provide information as to the family a protein may belong to, they still do not necessarily predict a function. The SEL1 protein, as evidenced by Biunno et al., does not have a specific known function, and is being investigated further to determine what its function and activities are. The skilled artisan would not be able to predict the activities or function of the NHP protein based on 46% similarity to the SEL1 protein, because the SEL1 protein also has no known activity, and only ***may*** have an association with diabetes mellitus type I.

There is no nexus between any of the diseases or disorders and the molecules of the instant invention. Given no disease state or any other function or activity known for the proteins, the proteins are not considered to have utility. In *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus.

Ct,.1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. Clearly, further research would be required to identify a disease that is associated with the claimed molecules or a "real world" use. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct,.1966), noting that a "patent is not a hunting liscense. It is not a reward for the search, but compensation for its successful conclusion." The instant claims are drawn to a polynucleotide encoding a protein which has undetermined function or biological significance, and the use of a protein to discover its receptor or properties does not constitute a specific, substantial utility. All of the biological activities of a protein need not be known to obtain a patent, but there must be some specific and substantial activity or function known. It is possible that after further characterization, this protein might be found to have a patentable utility, in which case the polynucleotides encoding the protein would have a specific utility, or the polynucleotides might be found to be associated with a specific disease. This further characterization, however, is part of the act of invention, and until it has been undertaken the Applicants' claimed invention is incomplete.

Claim Rejections - 35 USC § 112

Claims 1-8 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

A. Do claims 1-8 lack a Patentable Utility?

Beginning at page 4 of the Brief, Appellants point out that a sequence that is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists wholly unaffiliated with Appellants as a Novel Protein similar to SEL1L (Sel-1supressor of lin-12, C. elegans)-like) (GenBank accession number: Q9UGD3, alignment and GeneBank report provided in Exhibit A, also shown in Exhibit C and D of the response filed Sept. 16, 2002), is 99.8% identical over a 506 amino acid overlap to a described sequence (amino acids 184-689 of SEQ ID NO: 2 of the instant invention). Appellants argue that given this clear evidence that those skilled in the art have independently identified the sequences of the present invention as encoding a protein similar to SEL1, a well-established *Notch* ligand, there can be no question that Appellants' asserted utility for the described sequences is "credible", and as such, the scientific evidence of identity at both the amino acid and nucleic acid levels clearly establishes that those of skill in the art would recognize that sequences of the present invention as a human *Notch* ligand, a class of proteins with well known function, and therefore Appellants have described a utility in full compliance with the provisions of 35 U.S.C. § 101.

Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. First, while the protein of SEQ ID NO: 2 of the instant invention may be 99.8% identical to a protein identified in the art as Novel Protein ***similar to*** SEL1L, the protein of SEQ ID NO: 2 of the instant invention is only 46% identical to SEL1L itself; and is therefore 54% divergent. It is credible that the proteins of the instant invention are indeed similar to SEL1 and are probably in the *Notch* ***family***, but given the high level of amino acid divergence, do not necessarily bind *Notch* or have the same activities. Second, the *Notch* ***family*** ligands have very diverse functions, as discussed below. Therefore, similarity to SEL1 does not necessarily lend a specific and substantial utility and the credibility of the similarity is not questioned.

On page 5 of the brief, Appellants assert that two review articles cited in the Advisory Action mailed 12 August 2003 clearly support Appellants' assertions made in the specification, which states that "Because of the diverse activities that have been associated with *Notch* signaling pathways, *Notch* receptors, and their associated ligands and antagonists have been subject to intense scientific scrutiny." Appellants also on page 5 quote from the specification, which teaches that SEL-1 proteins are negative regulators of *Notch* family receptors, *Notch* receptors and their associated signaling pathways have been associated with development, apoptosis, neuron growth and maintenance, and genetic alterations in *Notch* receptors and their ligands have been associated with the numerous multiple human processes and disorders listed on page 5 of the brief (such as diabetes, cancer, stroke, Alzheimers, etc.), and that therefore the utility of *Notch* proteins and ligands are therefore clearly well-known to those of skill in the art.

Appellant's arguments have been fully considered but are not deemed to be persuasive. The references cited in the Advisory Action, Baron et al., Molecular Membrane Biology, 2002, Vol. 19, pages 27-38, Portin, P., Hereditas, 2002, Vol. 136, No. 2, pages 89-96 and Baron et al., Seminars in Cell and Developmental Biology, April, 2003, Vol. 12, No. 2, pages 113-119, provide support that classification of a putative ligand as a member of the *Notch* ligand family does not automatically confer a specific and substantial utility to the newly identified ligand. The references teach that there are different *Notch* family ligands that bind to different *Notch* family receptors that are expressed in different cell types and have different activities, and that *Notch family* signaling pathways are very complex. For example, apoptosis (programmed cell death) and neuron growth and maintenance, activities associated with *Notch* receptors and ligands, are opposite activities. The specific activities associated with *Notch* family members are dependent upon the protein and the cell or tissue it is expressed in. Also, the diseases or disorders associated with genetic alterations in *Notch* family receptors and their ligands are also protein specific. Therefore, the utility of any ***particular*** *Notch* ***family*** ligand is not well-known to those of skill in the art based on sequence homology, absent any evidence of functional activity.

On pages 5-6 of the brief, Appellants dispute that the Yan et al. paper cited in the Final Action does not support the alleged lack of utility, since this paper cites only one example, and although the ligands that differ by only two amino acids bind to two different receptors, the receptors are related, and one of the receptors was correctly identified as a member of the tumor necrosis family receptor superfamily based solely on sequence similarity. First, the paper of Yan et al., while citing only one example, clearly demonstrates that the unpredictability of the functions of proteins solely based upon sequence homology. While the two receptors bound by

the two isofroms of ectodysplasin are related, i.e., belonging to the TNFR superfamily, they clearly have different activities (See, e.g., page 524, column 3) and are distinct receptors. Even the title of the paper clearly states that the two receptors bound by the two isoforms are distinct. Secondly, while the EDA-A2 receptor was initially identified as a member of the TNFR superfamily solely based on sequence similarity, as Appellants argued, the biological functions of the receptor were not identified. In fact, Yan et al. performed extensive experimentation as described in the paper to define the ligand and biological activies of the EDA-A2 receptor. This type of experimentation is part of the invention process. As taught by Yan et al., members of the TNFR superfamily are involved in a number of physiological and pathological response by activating a wide variety of intracellular signaling pathways (beginning of page 523). The EDA-A2 receptor (XEDAR) fails to bind many known ligands of the TNFsuperfamily (1st column of page 524). Therefore, even if sequence analysis could assign a given protein to a protein family, the protein does not necessarily possess the same functions of a given member of the family. Consequently, the protein does not have a substantial utility because the biological function or activity is not defined and determining such a biological function of the protein would require significant further research, as demonstrated by Yan et al.

On page 6 of the brief Appellants also not that the series of older articles cited in the Final Action to support the proposition that function cannot be predicted based on structural information do not refer to *Notch* ligands. That the references do not refer to *Notch* is not relevant. The references were cited as evidence that even closely related proteins known to be in the same family of proteins can have different and even opposite activities. On page 6 of the brief Appellants cite a quote from Ji et al.,"a substantial degree of amino acid homology is found

between members of a particular subfamily", and assert that this quote suggests that homology with members of a G-protein coupled receptor is indicative that the particular is in fact a member of that family and supports Appellants assertion that a structure-function relationship is well-established. These arguments have been fully considered but are not deemed persuasive because the issue is not whether a protein can be assigned to a particular protein family based on sequence similarity or structural similarity, it is that the ***specific function*** of a new member of a protein family cannot be predicted based on this similarity. The Examiner notes that the critical issue at dispute is not a matter of whether the present nucleic acids encode a *Notch* family ligand; rather, it is a matter of whether the ligand encoded by present nucleic acids have defined biological functions and have a patentable utility. While a protein's structure can predict that it is a member of the G-protein coupled family (for example) and can be assumed to function as a receptor, the specific activity of that receptor cannot be predicted; what ligand the receptor binds to, what signal transduction system is utilized, what effect binding the ligand has on the cell, etc. Similarly, sequence similarity to a family of ligands does not render the present invention a specific and a patentable utility because there is no single-well established utility for the *Notch* ligand family due to the diversity in structures and functions of the ligands, and such functions of a ligand have to be determined experimentally.

On pages 6-7 of the brief Appellants assert that (these articles are just examples of the few spurious articles that) the PTO has repeatedly attempted to use spurious articles to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatics predictions, and Appllents agree that there is not 100% consensus within the scientific

community regarding prediction of protein function from homology information, and further agree that prediction of protein function from homology information is not 100% accurate. However, Appellants argue that the lack of 100% consensus on prediction of protein function from homology information is irrelevant to the question of whether the claimed nucleic acid sequence has a substantial and specific utility, and that 100% accuracy of prediction of protein function from homology information is not the standard for patentability under 35 U.S.C. § 101. Appellants point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be believable, and that the overwhelming majority of those of skill in the relevant art would believe prediction of protein function from homology information and the usefulness of bioinformatics predictions to be powerful and useful tools, as evidenced by the extensive number of journal articles which support Appellants' assertion that the overwhelming majority of those of skill in the art place a high value on prediction of protein function from homology information and the usefulness of bioinformatics predictions, and would thus believe that Appellants' sequence is a CUB containing protein. Appellants further argue that the asserted utility for the described sequences is credible, and that according to the Examination Guidelines for the Utility Requirement, if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., it has a specific and substantial utility), and the assertion would be considered credible by a person of ordinary skill in the art, and the Examiner should not impose a rejection based on lack of utility.

These arguments have been fully considered but are not deemed persuasive. First, there is no disclosure in the specification that the nucleic acids of the instant invention encode a CUB domain-containing protein. The instant specification teaches nucleic acids that encode a protein

similar to SEL-1. If it did encode such, it would still not be predictive of utility because there is no disclosure of what a CUB domain-containing protein is or what it's activity would be. Second, the issue is not that one of ordinary skill in the art would not find the uses for the nucleic acids or encoded protein believeable or credible, it is that there is no ***specific or stubstantial uses*** *asserted* for the nucleic acids or encoded protein. A number of general uses are listed, for example on page 14, lines 25-33, which include the generation of antibodies, reagents in diagnostic assays, identification of other cellular gene products related to the protein, as reagents in assays for screening for compounds that can be pharmaceutical reagents useful in therapeutic treatment of mental, biological or medical disorders. Utilities that would appear to be more specific and substantial are implied by the statement on page 14, lines 20-22 of the specification, "Given their structural relatedness to *Notch* ligands, the described NHPs are suitable for use and modification as contemplated for other *Notch* ligands and antagonists." However, as discussed above, the different members of the *Notch* ligand family have different activities, and therefore, this is neither a specific or substantial assertion.

Appellants on page 7 of the brief argue that a reason included for the alleged lack of utility is that the specification contained no working examples of any kind, and the this emphasis is misplaced as it has long been established that "there is not requirement for the disclosure of a specific example". Appellants assert that the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Appellants asserted utility. These arguments have been fully considered but are not deemed persuasive. The specification on page 3, lines 1-4 and page 13, lines 21-27, assert that the compounds of the instant invention could be

used as treating or preventing biological disorders, including, but not limited to, diabetes, heart disease and cancer, Alzheimer's Disease, neurodegenerative diseases such as Parkinson's disease. Stroke, vascular dementia, and conditions requiring modulation of fat and cholesterol metabolism such as coronary artery disease. Due to the lack of any kind of disclosed association between the molecules of the instant invention and diverse diseases listed, one of ordinary skill in the art would not find it believable that the molecules of the instant invention could diagnose, prevent or treat all of these different diseases, based on the lack of any correlative information in the specification and knowledge of the state of the art. A stated belief that a correlation exists between the molecules of the invention and any number of diseases is not sufficient guidance to use the polynucleotides or polypeptides to treat and/or diagnose a particular disease: it merely defines a starting point for further research and investigation. Therefore, the asserted utilities are not specific and substantial.

On pages 8-12 of the brief, Appellants assert that the prior office actions seem to be requiring Appellants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications that meet the requirements of 35. U.S.C. § 101, and that knowledge of the exact role of function of the presently claimed sequences are not required to track expression patterns using a gene chip. Appellants further assert that the present described novel sequence would have great utility in such gene DNA chip applications, and that the claimed sequences provide a specific marker of the gene encoding a testis specific *Notch* ligand, and such specific markers are targets for discovering drugs that are associated with human disorders and diseases such as diabetes, heart disease and cancer, and compositions that enhance the utility of such

DNA gene chips, must in themselves be useful. Appellants further assert that additional evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry based on the use of gene sequences or fragments thereof in a gene chip format, and cite a number of companies that have concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, and that the "real world" substantial industrial utility of gene sequences or fragments would, therefore appear to be widespread and well established, and have both scientific and commercial utility.

This has been fully considered but is not deemed to be persuasive for the following reasons: First, Appellants mischaracterize the Examiners' position as requiring Appellants to identify the biological role of the nucleic acid or function of the protein encoded by the presently claimed polynucleotides before the present sequences can be used in gene chip applications. The biological role of a polynucleotide or encoded protein is not required to render a gene chip useful, and it is not disputed that gene chip technology is a well established utility currently being exploited by a number of companies to determine correlations between expression patterns of nucleic acids and diseases. The Examiner would like to draw the Board's attention to the definition of the terms "a gene chip" mentioned in the Brief and in the instant specification by the Appellant. A gene chip is a customized device in biomedicine that allows researchers to detect, simultaneously, the presence and activity patterns of tens of thousands of DNA sequences. A gene chip can be used by researchers to describe the genetic malfunction associated with a disease, detect the presence of the disease in a particular patient, calculate a patient's genetic predisposition to that disease or identify the medicines likely to be most effective in treating a particular patient with the disease. A correlation is required between altered

expression of a nucleic acid and a particular disease or disorder; otherwise experimentation is required to determine what genes are altered in which diseases. The point is that while a set of nucleic acids in a chip may have utility as a group, a single member of that group does not necessarily have a specific and substantial utility. If the claimed compound is only useful as part of a larger mixture of compounds, then it is the mixture, and not the individual compounds, which have utility. Appellants' argument on page 9 of the brief that as only a small percentage of the genome actually encodes exons, which in turn encode amino acid sequences, not all human cDNA sequences are useful in such gene chip applications, and that this further discounts the Examiner's position the such uses are "generic" has been fully considered, but not deemed persuasive, because as discussed above, the Examiner acknowledges that gene chip technology has utility. However, the utility of gene chips is the combination of sequences, and not a single sequence, and if as asserted any nucleic acid encoding a protein has utility because it would enhance the utility of a DNA gene chip, this is not a specific and substantial utility for any single nucleic acid sequence present in the chip.

On pages 11-12 of the brief Appellants point out that the used of the claimed nucleic acid sequences have the greatest specific utility in gene chip applications once the role of the sequences has been identified, as have tissues of interest, as in the present case, and that one the role of the particular nucleic acid is known, the level of gene expression has an even greater significance. Appellants' arguments have been fully considered but are not deemed persuasive for the following reasons. The instant specification and brief assert that the nucleic acids of the instant invention are specifically expressed in testis. It has not been established that the claimed nucleic acid sequences are expressed at altered levels or forms in a specific diseased tissue as

compared with the corresponding healthy tissue. If the claimed nucleic acid molecules were in a gene chip and a compound caused decreased expression of the claimed nucleic acids, what would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to acerbate an unspecified disease? If it had been disclosed that the claimed nucleic acids are expressed at a higher level in a particular diseased tissue as compared with the corresponding healthy tissue, then the skilled artisan would infer that a compound that decreased expression of the nucleic acid molecule might be a good drug candidate that targets the disease. However, such would still require substantial further experimentation and it is not the case here. In addition, the claimed nucleic acid molecules may very well be expressed at equivalent levels in healthy tissues. If that were the case, then the compound would not be a good drug candidate. The claimed nucleic acid molecules may also very well be expressed at a lower level in a particular diseased tissue as compared to the corresponding healthy tissue. Then a compound that decreased expression of the claimed polynucleotides would *not* be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed nucleic acid molecule as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed nucleic acid molecules (or proteins encoded by the nucleic acids) and any diseases or disorders, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. Thus, the disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

There is no doubt that a gene chip (or DNA chips) is a valuable tool in gene expression monitoring and drug discovery. However, the claims are not drawn to the technique, rather to nucleic acid molecules which have not been disclosed as being associated with any particular diseases or conditions by its being expressed at an altered level or form in a specific diseased tissue as compared to the corresponding healthy tissue. Any nucleic acid molecules could be added to a gene chip. The use of the claimed uncharacterized nucleic acid molecules in such studies would have provided no more informative information than the use of any other unidentified nucleic acids. Thus, this asserted utility is not specific. Determining the relationship between the claimed nucleic acid molecules and any specific diseases or disorders would require significant further research. Therefore, this asserted utility is also not substantial.

On pages 10-11 of the brief Appellants assert that as a further example of utility is the use of the present sequences in such diagnostic assays as those associated with identification of paternity and forensic analysis, among others, and that the sequences of the present invention have particular utility as the application as filed identified several polymorphisms (page 14, lines 6-11). Appellants submit that even in the worst case scenario, the described polymorphisms are useful to distinguish 50% of the population, and that the skilled artisan would readily recognize and easily believe that the presently described polymorphic markers could be useful in forensic analysis, and the fact that forensic biologists use polymorphic markers every day provides more than ample support for the assertion that forensic biologists would also be able to use the specific polymorphic markers.

This has been fully considered but is not deemed to be persuasive for the following reasons. First, the specification describes only one polymorphic form besides that of the nucleic

acid of SEQ ID NO: 1, and there is no information about the incidence of the polymorphism in any population. Second, even though such polymorphisms could distinguish between different individuals in a population, this would not be a specific and substantial utility. Any gene can have any number of polymorphisms, if DNA from enough individuals is analyzed, and any such gene could be used for forensic analysis. If a particular polymorphism for the claimed nucleic acids was very rare, this could be useful in identifying an individual carrying this rare polymorphism. However, the specification does not disclose the frequency of the polymorphism, and absent this information, the instant nucleic acids would not be informative. As an example of polymorphisms having specific and substantial utility are HLA (human leukocyte antigen) polymorphisms. Baxter-Lowe et al., U.S. Patent No. 5,468,611 state in column 2, lines 39-59:

"Successful bone marrow transplantation depends on the degree of HLA matching between donor/recipient pairs. This results from the physiological role of human lymphocyte antigens in self-restriction of cellular interactions during and immune response. See Schwartz, Ann. Rev. Immunol. 3:27-261, 1985. If polymorphic residues in the HLA proteins are mismatched, the immune system may recognize the cells bearing the mismatched HLA as foreign. The consequences of such mismatching include graft-versus-host disease (GVHD), graft rejection, and failure to reconstitute a competent immune system. See Hows, Bone Marrow Transplantation, 1:259-264. These problems are minimized by selection of HLA-matched siblings as donors. Unfortunately, this option is available for only about 30-40% of patients who could benefit from a bone marrow transplant. In the remaining patients (60-70%), HLA typing with high resolving power is necessary for selection of an optimally matched, unrelated donor. More than 40 variant HLA-DR beta alleles have been identified among the population, and more are being identified on an ongoing basis."

Therefore, these HLA polymorphisms have a specific, substantial and real world utility, which is not the situation in the present case.

Appellants argue on pages 11-12 of the brief that nucleic acid sequences have the greatest specific utility in gene chip applications once the role of the sequence has been identified, as have tissues of interest, as in the present case, and that the requirement for a specific utility should not be confused with a unique utility, which is clearly an improper standard.

Appellant's arguments have been fully considered but are not deemed to be persuasive for the following reasons: First, Appellant is mischaracterizing the examiner's position regarding the requirements for a specific utility. There is no dispute on the case law itself. The issue at dispute is what constitutes a specific utility. A specific utility is a utility specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. To satisfy the utility requirement under 35 U.S.C. § 101, a utility does not need to be unique; however, it must be specific. The use of the present nucleic acid in tracking gene expression patterns on a gene chip is not specific, both because contrary to Appellants' assertions, the physiological role of the claimed sequence is not known, and because such a use would be applicable to any cDNA. Furthermore, as noted above and in the final rejection, such uses are all considered research uses only designed to identify a particular function of the claimed molecules and are not a substantial utility. Thus, the asserted use is not specific and substantial.

It is further noted that the patents on batteries, automobile tires, golf balls, and treatments for a variety of human diseases are issued by the USPTO because the invention in each patent has a specific and substantial utility, not simply because the claimed subject matter is related to

batteries, automobile tires, golf balls, or disease treatment. For example, a golf ball can be used; a compound has a particular property that can be used to treat a specific disease, e.g., prostate cancer. That is not the case here.

Appellants' assert on pages 12-14 of the brief that only one utility is needed to meet the requirements of 35 U.S.C. § 101, and that the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome. Appellants further present Exhibit J, which shows the result of a blast (sequence alignment) analysis using SEQ ID NO: 1 of the present invention when compared to the identified human genomic sequence, and which indicates that the sequence of the present invention is encoded by 20 exons spread non-contiguously along a region of human chromosome 20.

Appellants' arguments have been fully considered but are not deemed to be persuasive, because such a utility is considered a research use only designed to identify a particular function of the claimed sequences and is not a specific or substantial utility, i.e., is not a use of the invention. See, e.g., *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein such a research use was not considered a "substantial utility." Such a use of the polynucleotide sequences in gene mapping does not represent a specific and substantial utility. The exhibit and the publication cited by the Appellant merely show that the significance of expressed sequences in the structural analysis of genomic data; they do not show that the present polynucleotide sequences have a patentable utility.

Beginning at the top of page 14 of the Brief, Appellant summarizes case law on the utility requirement. Citing case law, Appellant urges that the present claims clearly meet the

requirement of 35 U.S.C. §101. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility.

Appellants' arguments have been fully considered but are not deemed to be persuasive for the following reasons. First, the statement, "(t)o violate §101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), indicates that a rejection under 35 U.S.C. § 101 *for lack of operability* can be overcome by a showing of actual use or commercial success. The claimed invention in the instant case is drawn to nucleic acid sequences, not a device; the instant rejection under 35U.S.C. §101 is not directed to inoperativeness of a device, rather to a lack of patentable utility of the claimed nucleic acid sequences; and the instant issue is whether the asserted utilities meet the three-pronged test for a patentable utility.

Secondly, since the specification fails to disclose a specific, substantial utility or a well-established utility, the present claims do not satisfy the utility requirement of 35 U.S.C. §101. Merely citing case laws on the utility requirement does not render a patentable utility for the present invention. While "anything under the sun that is made by man" is patentable, it does not necessarily mean the present invention is patentable. In fact, the present invention is not patentable due to lack of a patentable utility.

Furthermore, while the FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws, and the requirement for the utility of the claimed invention is different from the FDA standard for drug approval, 35 U.S.C. §101 does require a specific, substantial, and credible utility, or well-established utility for an invention. Such a utility has to be a "real world " context of use which does not require significant further research.

Appellant confuses this requirement with the "further research and development" needed in pharmaceutical composition and drug development. In other words, a patentable utility has to be clearly identified or immediately apparent in the specification, whereas some "further research and development" is permitted in drug development. For example, determining optimal dosages or drug tolerance in human is further research and development, which is acceptable under 35 USC 101 because it is not significant. On the other hand, determining a specific disease to be treated by a drug constitutes significant further research and development, which is not acceptable under 35 U.S.C. §101.

In the instant case, the specification fails to disclose the biological functions, physiological significance, or any specific and substantial utility of the claimed molecules. Without such information, one in the skilled art cannot use the claimed invention in a meaningful manner. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

It is further noted that the instant application was filed November 16, 2000. No evidence on the specific biological functions or physiological significance of the molecules of the present invention has ever been brought forth in an appropriate form during the prosecution history. This supports the Examiner's position that significant further research or undue experimentation is required to identify such information.

Finally, at pages 15-16 of the Brief, Appellants challenge the legality of the Patent Examination Utility Guidelines and the validity of issued US patents. The Examiner has no authority to comment on the legality of the Guidelines and the validity of US Patents.

For the above *reasons, it is believed that the rejections should be sustained. Appellants' arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie* case of lack of utility and it is believed that the rejections should be sustained.

B. Are Claims 1-8 Unusable Due to a lack of Patentable Utility?

As Appellants indicate at page 17 of the Brief, a rejection under U.S.C. § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under 35 U.S.C. § 101.

Therefore, for reasons set forth above, Appellant's arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the *prima facie* case of lack of utility.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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December 27, 2003

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